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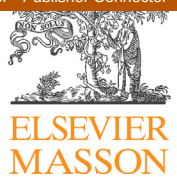

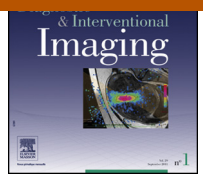

ORIGINAL ARTICLE / *Breast imaging*

A single-institution study of 117 pregnancy-associated breast cancers (PABC): Presentation, imaging, clinicopathological data and outcome

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KEYWORDS
Breast;
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Abstract
Background: This retrospective single-institution study was designed to describe the main clinical, radiological and histological features, as well as the outcome of pregnancy-associated breast cancer (PABC), with a special emphasis on imaging and diagnostic difficulties.
Material and methods: We reviewed all breast cancers diagnosed during pregnancy or during the 12 months following delivery at our institution, between 1993 and 2009. Out of a total of 16,555 new cases of breast cancer observed during this period, 117 PABC (0.7%) were diagnosed.
Results: Mean age at diagnosis was 33.7 years. Most cancers (81.2%) were diagnosed after delivery. Intermediate or high family risk was frequent (27.5%). The most common mode of presentation was a palpable mass (89.7%). Mean time to diagnosis was 5.8 months. Sensitivity for mammography was 80.9% and for ultrasound 77%. Most prognostic factors were unfavourable: frequent lymph node involvement (51.8%), high-grade tumours, hormone receptor negativity (45.9%) and HER2 positivity (38.7%). Treatments generally included surgery (61.7% mastectomies), radiotherapy (96%) and chemotherapy (79.6%). Overall 5-year survival was 81.8%.
Conclusion: PABC is an uncommon but aggressive form of breast cancer and must be considered in the presence of any breast abnormality during pregnancy or the months following delivery.

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Mammography and ultrasound should both be performed at the slightest clinical suspicion. Radiologists must be aware that masses may lack typical malignant ultrasound characteristics. Biopsies should be largely performed.
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Abbreviations

PABC	Pregnancy-associated breast cancer
TNM	Tumor, node, metastasis
BI-RADS ACR	Breast Imaging Reporting and Data System of the American College of Radiology
TOP	Termination of pregnancy
DCIS	Ductal carcinoma in situ
IDC	Invasive ductal carcinoma
ILC	Invasive lobular carcinoma

Introduction

Pregnancy-associated breast cancer (PABC) is defined as the development of breast cancer during pregnancy or during the 12 months following delivery. It occurs in 1/3000 to 1/10,000 pregnancies [1]. The incidence of PABC is increasing in industrialized countries, as women tend to postpone maternity [2].

PABC are serious cancers for several reasons: young age of the patients, frequently delayed diagnosis, often advanced stage and aggressive histological profile, although whether PABC is more serious than other breast cancers at an equivalent stage and with equivalent prognostic factors has not been clearly determined [3—5].

This retrospective study, based on a large number of cases with long-term follow-up, was designed to describe the main clinical, radiological, and histological features, as well as the outcome of pregnancy-associated breast cancer, with a special emphasis on imaging and diagnostic difficulties.

Materials and methods

This retrospective descriptive study included all patients with breast cancer diagnosed during pregnancy or during the 12 months following delivery treated at René-Huguenin Hospital — Institut Curie between 1st January 1993 and 31st December 2009. The study was approved by the Curie Institute/René-Huguenin Hospital ethics committee.

Out of a total of 16,555 new cases of breast cancer observed during this period, including 1958 patients between the ages of 20 and 43 years, 117 cases of PABC (0.7%) were diagnosed.

The study population comprised 113 patients, including 4 patients with synchronous bilateral breast cancer, i.e. a total of 117 cancers. Two authors (AL, MM) reviewed all of the computerized medical charts. The imaging was most of the time performed in various external institutions, and was reviewed by a senior breast-specialized radiologist of our institution in 73 of the 117 cases. When mammography and sonography had not been reviewed at our institution and the imaging was no longer available (44 cases, mostly from 1993 to 1999), we relied on the medical reports. We visualized MRI when performed, but we did not include these results in this study as they concerned only 15 patients.

The following elements were analysed: clinical setting (age at diagnosis, history), date of diagnosis, circumstances of discovery, clinical examination according to the TNM classification, inflammatory signs (erythema and oedema), time for diagnosis, imaging data (mammography and ultrasound), histological results, treatment regimen and follow-up.

We established the familial risk for breast cancer according to Eisinger et al. [6] We considered a score of 4 or more as high risk, a score of 3 or 2 as intermediate risk, and a score of 1 as not significant.

Imaging abnormalities were classified according to the criteria of the Breast Imaging Reporting and Data System of the American College of Radiology (BI-RADS ACR) [7]. ACR categories 1, 2 and 3 were considered to be negative and ACR categories 4 and 5 were considered to be positive.

Survival analyses were performed using the Kaplan—Meier method with R 2.10.1 software.

Results

The study population comprised 113 patients, four of whom had synchronous bilateral breast cancer, i.e. a total of 117 cancers. Most results are presented in tables: clinical data (Tables 1 and 2), imaging (Table 3) and histology (Table 4).

The mean age at diagnosis was 33.7 years (range: 24—42 years).

Out of the 69 patients for whom we had family history data, 19 patients (27.5%) had intermediate or high risk factors, the other 50 patients had low or no family risk.

Eight patients (accounting for 10 cases, as two of them had synchronous bilateral cancer) out of the 113 patients had mutations (*3BRCA2* and *5BRCA1*). Only one patient was known for the mutation when the breast cancer was diagnosed, she and 4 other patients were at high risk. One mutated (*BRCA2*) patient with bilateral breast cancer was at intermediate risk and 2 patients with proven mutations had no familial risk (the genetic enquiry was done because of their personal history).

The mean time from first symptom to histological diagnosis was 5.8 months.

Among the 21 patients in whom breast cancer was diagnosed during pregnancy, termination of pregnancy (TOP) was performed in 10 cases (9/10 during the first trimester).

Mammography (Table 3) showed a mass (without or with microcalcifications) in 55.1% of cases, and microcalcifications in 55% of cases (isolated or associated with mass, architectural distorsion or focal asymmetry) (Fig. 1).

Table 1 Clinical setting, date of diagnosis and circumstances of discovery.

Variables	*n*	%
Familial risk[a]		
Absent or low	50	72.5
Intermediate	9	13
High	10	14.5
Date of diagnosis		
During pregnancy (mean term: 3.9 months)	22	18.8
After pregnancy	95	81.2
≤ 12 months after delivery	80	68.4
> 12 months after delivery (delayed diagnosis)	6	5.1
≤ 12 months after TOP, SM or FD	9	7.7
Circumstances of discovery		
Palpable mass	105	89.7
Subclinical lesion (detected on imaging)	9	7.7
Inflammatory breast	2	1.7
Nipple discharge	1	0.9

TOP: termination of pregnancy, SM: spontaneous miscarriage, FD foetal death.
[a] Data available for 69 patients.

Table 2 TNM classification.

T[a]	Number of cases (%)	N[b]	*n* (%)	M	*n* (%)
T0	12 (10.7)	N0	57 (52.8)	MO	110 (94)
T1	20 (17.9)	N1	42 (38.9)	M1	7 (6)
T2	39 (34.8)	N2	8 (7.4)		
T3	27 (24.1)	N3	1 (0.9)		
T4[c]	14 (12.5)				

T: tumour size, N: lymph node involvement, M: metastases.
[a] Data available for 112 patients.
[b] Data available for 108 patients.
[c] Including 10 T4d cases.

Ultrasound (Table 3) was usually abnormal, with a mass or a suspicious focal zone in 89.2% of the cases (Fig. 2), but it was sometimes normal and some masses were classified as probably benign (ACR3), because of regular borders, posterior acoustic enhancement, or parallel orientation (Fig. 3).

The majority of patients (90 out of 113) received chemotherapy (79,6%) and underwent radiotherapy (84,2%). Neo-adjuvant chemotherapy was done for 53 patients; the rest (37 patients) had adjuvant chemotherapy. Almost all patients (91.5%) underwent surgery (except those who presented with metastatic disease at diagnosis), with a majority of mastectomies (61.7%) because of tumor size and/or multifocality.

Six patients (seven cancers) presented metastatic disease at diagnosis. One had bone metastasis, one had nodal (other than axillary) metastasis, the four other patients had multiple site metastasis. Three of them had died and the other three were alive at the end of the study.

Table 3 Type of abnormality and BI-RADS classification.

Variables	*n*	%
Mammographic abnormalities[a]		
Mass (without/with microcalcifications)	49 (21/28)	55.1
Asymmetric density (without/with micros)	9 (3/6)	10.1
Architectural distorsion (without/with micros)	5 (5/0)	5.6
Isolated microcalcifications	15	16.9
Normal	11	12.3
Mammographic classification		
ACR Bi-Rads 1/2/3	17	19.1
ACR Bi-Rads 4/5	72	80.9
Type of ultrasound abnormality[b]		
Mass	63	85.1
Isolated attenuation/heterogeneous zone	3	4.1
Normal	8	10.8
Ultrasound classification		
ACR Bi-Rads 1/2/3	17	23
ACR Bi-Rads 4/5	57	77

[a] Data available for 89 patients.
[b] Data available for 74 patients.

The median follow-up, available for 112 patients, was 61 months (range: 6—211 months). Survival curves were plotted for initially M0 patients (107 patients).

Five-year survival [95% CI] was: 81.8 [74.2; 90.1] for overall survival, 56.5 [47.1; 67.7] for disease-free survival, 74.4 [65.7; 84.3] for locoregional relapse-free survival and 72.5 [63.8; 82.3] for metastasis-free survival.

Twenty-three of the 107 (M0) patients died and 46 experienced an event: 15 experienced isolated local relapse, 20 experienced a metastatic event, and 11 experienced both local relapse and a metastatic event. Metastatic events concerned several sites in 53.3% of patients, bone only in 16.7%, liver only in 10%, and other sites in 20% of cases.

Discussion

PABC is an uncommon disease, as, over a 16-year period in our institution, it represented 6% of all breast cancers in the 20—43 years age group (which represent only 11.8% of all breast cancers). This proportion is consistent with that reported by Andersson et al. (7%), while Genin et al. reported a higher proportion (14.5%) [2,8].

For this reason, large series are difficult to obtain. Many studies reported in the literature are multi-institutional, in particular, the study by Bonnier et al., comprising 154 patients derived from 23 centres in France [5] and another study of 130 PABC diagnosed during pregnancy, prospectively collected from an international registry [9]. To our knowledge, the principal single-institution studies reported

Table 4 Histological data.

Variables	*n*	%
Type of cancer[a]		
Invasive ± DCIS	95	84.1
DCIS + micro-invasion	14	12.4
Pure DCIS	4	3.5
Invasive histological type[b]		
Invasive ductal carcinoma	73	78.5
Invasive lobular carcinoma	4	4.3
Other	16	17.2
Invasive component grade[c]		
Grade 1	4	4.2
Grade 2	31	32.6
Grade 3	60	63.2
In situ grade[d]		
Low grade	0	0
Intermediate grade	15	26.8
High-grade	41	73.2
Hormone receptors[e]		
HR−	39	45.9
HR +	46	54.1
HER2[f]		
HER2 positive	24	38.7
HER2 negative	38	61.3
Axillary lymph nodes[g]		
pN−	53	48.2
pN+	57	51.8

Negative hormone receptors: ER− and PR−; positive hormone receptors: ER+ and/or PR+.
[a] Data available for 113 cases.
[b] Data available for 93 cases.
[c] Data available for 95 cases.
[d] Data available for 56 cases.
[e] Data available for 85 cases.
[f] Data available for 62 cases.
[g] Data available for 110 cases (N+ on pre-chemotherapy cytology or axillary dissection).

in the literature concerned 99 and 104 patients, respectively [4,10], but many were smaller [11—15].

Most of the breast cancers in our series were diagnosed during the post-partum period; only 18.8% were diagnosed during pregnancy. The mean age of onset was 33.7 years, which is consistent with the data reported in the literature [16,17].

Like other authors [18—23], we frequently found an intermediate or high family breast cancer risk (27.5%). Eight patients out of the 113 (7%) presented a *BRCA1* or *BRCA2* mutation (known in only one patient at the time of diagnosis, the others were diagnosed after the PABC was treated), which is why some authors recommend genetic screening in all cases of PABC [16]. This seems all the more important in view of the fact that in our study, in the group with mutations, two patients had no family history and one was only at intermediate risk. However, the majority of the young PABC patients did not have a significant family history of breast cancer and this diagnosis must therefore be considered in all cases.

The most common mode of presentation was a palpable mass (89.7% in our series), confirming the data of the literature [12,14,16,22—25]. Nevertheless, 7.7% of lesions (9 cases) in our series were subclinical. Imaging in these patients was performed systematically because of high or intermediate risk (5 of the 8 patients, accounting for 6 cases). In two cases, imaging was performed for mastodynia and another because of palpable masses due to cysts; in all three, mammography showed suspicious microcalcifications.

PABC were often advanced at the time of diagnosis, as high rates of large tumours (T3 + T4 = 36.6%), clinical lymph node involvement (N1 + N2 + N3 = 47.2%) and inflammatory lesions (9%) were observed. Other authors reported similar results [4,5].

The mean time to diagnosis in this series was 5.8 months, similar to that reported by most authors [12,22,26]. Delayed diagnosis, defined as an interval of ≥ 4 months following onset of symptoms, was observed for 40 (35.4%) of the 113 patients of this series, with a severely delayed diagnosis (≥ 12 months) for 15 patients (13.3%).

There are many causes for delayed diagnosis. Very often, neither the doctor nor the patient considers the possibility of a diagnosis of cancer, particularly during pregnancy, and tend to defer the investigations until after delivery. Diagnostic difficulties are also partly responsible for delayed diagnosis, as clinical examination or imaging may be considered to be benign and aspiration cytology may give false-negative results.

Breast palpation is difficult, as the breasts of young women are firmer, more nodular and hypertrophied, particularly during pregnancy and lactation, and it is not always easy to confirm palpation of a mass; breast inflammation can also be mistaken for simple puerperal mastitis.

Another difficulty comes from the reluctance of many doctors to request mammography for young women, and particularly during pregnancy. This is mostly due to fear of X-ray related risks. But mammography has been demonstrated to be a safe procedure, even during pregnancy, as irradiation to the foetus is negligible [14,27] Many think that mammography will not be contributory due to high breast density (related to the patient's young age and increased by pregnancy or post-partum). Actually the mass was seen in 55.1% of our cases, and even when the mass was not seen, mammographic signs in favour of the diagnosis are often present: microcalcifications in 55% of cases in our series, architectural distortion (5.6%) or focal asymmetry (10.1%). Mammography had a high sensitivity in our study (80.9%), comparable to that described by Liberman et al., while Ahn et al. and Yang et al. reported sensitivities of 86.7% and 90%, respectively [12,13,14].

Most authors consider ultrasound to be a very reliable examination in this setting, with sensitivity close to 100% [12—15]. According to current guidelines, it should be performed as first-line procedure [15,16]. However, in the present study, the sensitivity of ultrasound was lower, with an estimated value of 77%. We reviewed carefully the 17 cases with ultrasound ACR 1, 2 or 3.

Five of these cases were DCIS: 3 were pure DCIS, one was associated with very small (2 and 3 mm) invasive components and another with micro-invasion, which explains why ultrasound was negative. In 4 of these cases, we found typically

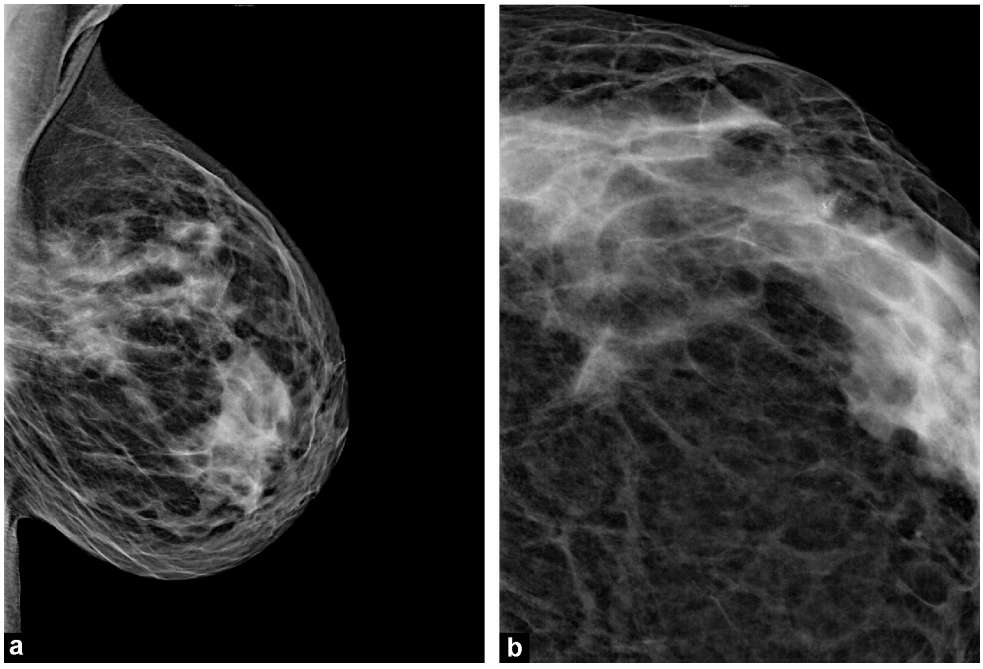

Figure 1. A 29-year-old woman, 11 months post-partum, no family history. Left breast mass T2N1. (a) Mediolateral and (b) magnified mediolateral mammograms show architectural distorsion with irregular microcalcifications highly suggestive of malignancy. Grade II invasive ductal carcinoma.

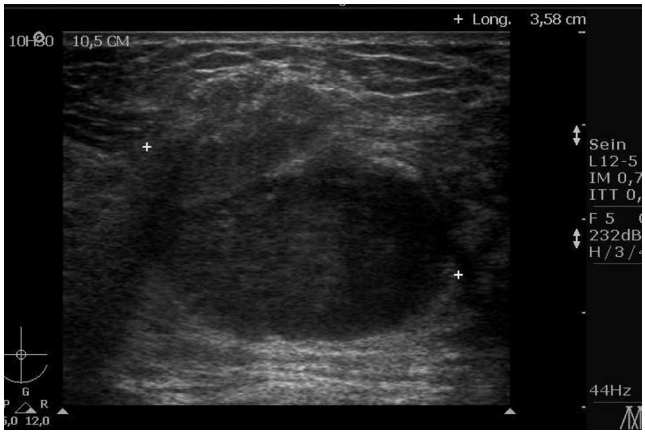

Figure 2. A 38-year-old woman, 5 months pregnant, right breast mass. Ultrasound shows a mass with parallel orientation, posterior acoustic enhancement, but borders are microlobulated and lateral part of the mass is irregular (ACR4). Grade III invasive ductal carcinoma.

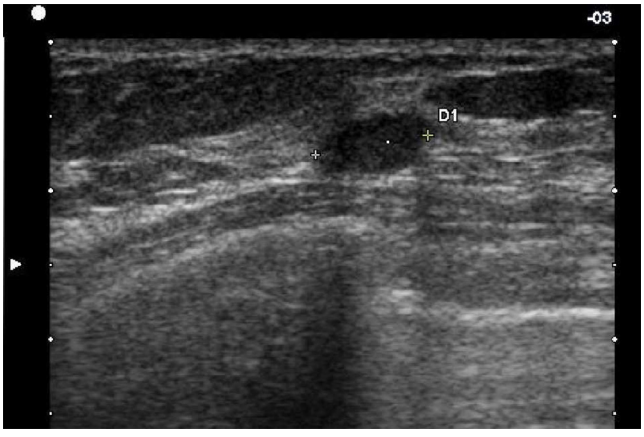

Figure 3. A 39-year-old woman, high family risk, 7 months post-partum. Ultrasound shows small oval, benign-appearing left breast mass (ACR3). Grade III invasive ductal carcinoma. Subsequent genetic inquiry revealed *BRCA1* mutation.

malignant microcalcifications on mammography, and the 5th patient had sero-hematic nipple discharge with multiple filling defects on galactography.

Three cases were due to small (6—7 mm) benign-appearing masses in two women with *BRCA1* mutations that were at histology grade 3, triple negative IDC (Fig. 3). Another case was particularly misleading, because it appeared as a subcutaneous 8 mm ectopic mobile mass. Both the clinician and the radiologist thought it was a sebaceous cyst, and surgery was performed at the request of the patient, showing a 6 mm grade 1 IDC.

We think those 9 cases were true normal (the 5 DCIS) and true ACR3 masses (4 cases).

The other eight cases were probably incorrectly classified as reassuring. One was a small axillary mass in a 27-year-old woman who had previous axillary node dissection for bilateral breast cancer three years before, so, the axillary area was difficult to examine with ultrasound (MRI was positive). Another case was a huge (100 mm) infiltrating inflammatory breast cancer in a patient who had previous breast surgery reduction. Ultrasound was considered insufficiently informative (mammography and MRI were positive). The most frequent situation (6 out of 8 cases) was a mass in a young woman ''resembling fibro adenoma''. Unfortunately, we could not review the images in these cases. Ultrasound examinations were derived from multiple sources and different machines, and patients were subsequently referred

to our institution. For the present study, we had to rely on the reports when the imaging had not been reviewed. It is one of the limitations of our study, but it also is noteworthy, as it corresponds to the ''real-life'' conditions of radiology practice. Ayyappan et al. [28] have reported that pregnancy-associated breast cancers can have a falsely reassuring appearance on ultrasound (parallel orientation in 58%, posterior acoustic enhancement in 63%). It is a pitfall radiologists must be aware of. Of course, the young patients' age can also be misleading, as benign pathologies are much more frequent in this category. If those 8 cases had been correctly classified ACR4 or 5, in an ideal set without margin of error, ultrasound sensitivity would have been at best 87.8% which is much better, but still not 100%.

Thus, the low sensitivity of ultrasound in our study is due to masses incorrectly classified as ''probably benign'', but also to DCIS, and to classical misleading cancers in BRCA1 patients.

Most breast disorders related to pregnancy are benign, but given the seriousness of PABC and the risk of a delayed diagnosis, all masses during this period must be carefully evaluated. After clinical examination, which should be systematically and regularly performed during pregnancy, US is the initial test in symptomatic women. If clinical examination is not suspicious and US aspect is typically benign, short-term follow-up may be considered. But in case of high-risk women, of indeterminate clinical and/or US results, mammography should be performed without hesitation. We found no PABC during pregnancy with both mammographic and US negative results. In cases of breast inflammation, if it does not disappear in a few days of appropriate medical treatment, mammography should be completed quickly by biopsy.

Biopsies must be obtained at the slightest doubt. Biopsy is more reliable than cytology (high false-negative and false-positive rates during pregnancy) [28—30].

We observed a similar rate of invasive ductal carcinoma to that reported in the literature and in breast cancer in general, but with a higher rate of undifferentiated carcinoma [3,5,16,18]. The proportion of invasive lobular carcinoma was lower than that observed in breast cancers in general (4.3% versus 10—15%) and pure DCIS was uncommon (3.5% versus 10 to 15%).

Most prognostic factors were unfavourable, as in previously published series, with a majority of high-grade tumours for the invasive component (63.2% grade 3) and for the in situ component (73.2% high-grade) and frequent lymph node involvement (51.8%) [4,5,17,18,31]. Hormone receptors were more frequently negative in PABC than in other breast cancers (45.9% versus about 30%), in line with the literature [4,5,18,31,32]. However, the positive hormone receptor rate may be underestimated by the usual techniques, especially during pregnancy, which is why some authors recommend the use of other techniques (pS2/TFF1) to more accurately determine hormone dependence and to optimize endocrine therapy [11].

A high rate of HER2 positive tumours was observed in this series (38.7% versus 15% for most series of breast cancers), as previously reported by some authors, but not by others [5,8]. However, HER2 status was available for 62 tumours but not for all, as this series began in 1993, and HER2 status was performed routinely only from 2002. The unfavourable characteristics could be attributed to the younger age of women with PABC. However, a recent case-control study showed that PABC is associated with unfavourable histological characteristics independently of age [4].

Due to poor prognostic factors and/or large tumours, the majority of patients received chemotherapy (79,6%) and underwent radiotherapy (84,2%). Almost all patients underwent surgery (except those who presented with metastatic disease at diagnosis), with a majority of mastectomies (61.7%) because of tumor size and/or multifocality.

Five-year overall survival for M0 patients was 81.8%. Whether the prognosis of PABC is similar to that of other breast cancers when matched for stage, age and histology, is still debated [4,5,9—11,17,18,23,26,33,34].

Numerous oncological, obstetric, and psychosocial parameters must be taken into account in the management of pregnancy-associated breast cancer. Termination of pregnancy (TOP) does not improve the maternal prognosis, but should be considered case by case, especially at the beginning of pregnancy and/or in the presence of a particularly severe form of cancer [9,35]. In our series, many patients had termination of pregnancy (10 out of 21). The diagnosis in those cases was made very early during pregnancy: 7 times during the first month (pregnancy was sometimes discovered when breast cancer was being assessed), 1 in the second month and 1 in the third month. The only patient who had TOP after the first trimester (5th month) was metastatic at diagnosis. For patients who went on with pregnancy, no adverse outcome was reported for the baby but early caesarean sections were frequent (5 patients).

Surgery can be performed at any time during pregnancy, radiotherapy and endocrine therapy are contraindicated, and chemotherapy can be administered from the second trimester onwards, the main risk for the infant being possible preterm delivery. Most studies do not report any significant toxicity at birth following maternal chemotherapy, but the long-term effects of chemotherapy have not been extensively studied.

Our study has several limitations. Due to the low frequency of PABC, this large series spreads over 16 years, during which imaging as well as treatments have changed a lot, accounting for heterogeneity in both these issues. We did not study the role of MRI (in the post-partum period), as only 15 patients had an MRI. But we found that clinical examination combined with ultrasound and mammography, and completed by biopsy when needed, can quickly resolve almost all cases. MRI will probably have a more important role in the future, if not for diagnosis itself, at least in a neo-adjuvant treatment setting for those young patients.

Conclusion

Although infrequent, PABC's incidence is growing, as the age of first pregnancy is continuing to increase. It is an aggressive form of breast cancer, with unfavourable histological and immunophenotypic characteristics. The diagnosis of PABC must be considered in the presence of any breast abnormality during pregnancy or during the months following delivery, even in the absence of family breast cancer history, to avoid delayed diagnosis, which is still a frequent problem. Imaging should be performed at the slightest clinical abnormality,

as mammography and ultrasound are both contributory and complementary. Radiologists must be aware that masses may lack typical malignant ultrasound characteristics, and that ultrasound can be negative in case of predominant DCIS. Biopsy must be preferred to cytology, which is often misleading in this setting.

Numerous parameters must be taken into account when breast cancer is diagnosed during pregnancy to protect the foetus as far as possible, without either under-treating or delaying treatment of the mother, hence, the value of multidisciplinary referral centres.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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